Critical Reviews in Oncology / Hematology 133 (2019) 58–73

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Targeting homologous repair deficiency in breast and ovarian cancers: Biological pathways, preclinical and clinical data

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ARTICLE INFO

Keywords:
Triple-negative breast cancer
Epithelial ovarian cancer
Homologous recombination deficiency
BRCAness
Prognostic biomarker
Predictive biomarker
Platinum salts
PARP inhibitor

ABSTRACT

Mutation or epigenetic silencing of homologous recombination (HR) repair genes is characteristic of a growing proportion of triple-negative breast cancers (TNBCs) and high-grade serous ovarian carcinomas. Defects in HR lead to genome instability, allowing cells to acquire the multiple genetic alterations essential for cancer development. However, this deficiency can also be exploited by using DNA damaging agents or by targeting compensatory repair pathways. A noteworthy example is treatment of TNBC and epithelial ovarian cancer harboring *BRCA1/2* germline mutations using platinum salts and/or PARP inhibitors. Dramatic responses to PARP inhibitors may support a wider use in the HR-deficient population beyond those with mutated germline *BRCA1* and *2*. In this review, we discuss HR deficiency hallmarks as predictive biomarkers for platinum salt and PARP inhibitor sensitivity for selecting patients affected by TNBC or epithelial ovarian cancer who could benefit from these therapeutic options.

1. Introduction

DNA is constantly suffering damage from environmental assaults and endogenous metabolic activities. The DNA damage response (DDR) consists of five main overlapping pathways that reinforce genomic integrity throughout the cell cycle and DNA replication. Homologous recombination (HR) repair is the main rescue pathway, in which double-strand breaks (DSBs) are repaired. BRCA1 and 2 are essential proteins involved in this pathway, and their deficiencies lead to genomic instability, a hallmark of cancer. This deficiency is also an Achilles' heel because *BRCA1*– and *2*–deficient tumors appear to be highly sensitive to DNA-damaging agents such as alkylating agents or platinum salts, which generate DSBs (Farmer et al., 2005). Moreover, these HR-deficient (HRD) tumors are better responders to agents that target compensatory repair pathways in a synthetic lethal approach compared to HR-proficient tumors. The increased benefit of platinum salts and poly ADP-ribose polymerase 1 (PARP1) inhibitors (PARPi) is well-known in germline *BRCA1/2*-mutated tumors (Bryant et al., 2005; Farmer et al., 2005). The percentage of BRCA mutations (germline and somatic) are similar in high-grade serous ovarian cancer (HGSOC) and basal breast cancer (BC) according to TCGA data (20%) (Cancer Genome Atlas Research Network et al., 2011; Cancer et al., 2012). However, these germline mutations account for a small percentage of HR deficiency, and HRD tumors could represent up to 50% of HGSOC (Cancer Genome Atlas Research Network et al., 2011) and more than 20% of basal BC (Cancer et al., 2012), leading to extensive use of PARPi and platinum salts beyond the *BRCA1/2* germline mutated tumors, but with more limited success. Because of the lack of well-defined biomarkers to characterize HRD status, every prospective trial testing platinum salts and PARPi includes a companion test with variable relevance.

In this three-part review, we first present the genes and pathways implicated in the DNA repair process and their germline and somatic mutations in human pathology. Second we assess the concept of *BRCAness* features, discussing their characteristics and how to better define this population. Third, we focus on the development of HRD biomarkers, their prognostic values, and their utility for predicting response to platinum and PARPi.

2. Methods

For the first and second parts of this review, we used the MEDLINE database to select articles published in English from 1985 to August 2017. The following keywords were entered: homologous repair

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https://doi.org/10.1016/j.critrevonc.2018.10.012
Received 20 March 2018; Received in revised form 25 September 2018; Accepted 30 October 2018

pathway, DNA damage, *BRCAness*, *BRCA1/2*, BRCA methylation, and genomic signature, including synonymous terms, and from references included in selected reviews (Jackson and Bartek (2009); Turner et al., 2004; Frey and Pothuri, 2017; Watkins et al., 2014; De Picciotto et al., 2016). These terms could be included either in article titles or in their abstract.

For the third part of this review, we performed searches on MEDLINE and the ASCO and San Antonio Breast Cancer (SABC) Symposium databases using the following keywords: *BRCAness*, HRD, *BRCA1/2* mutation, *BRCA* methylation, platinum salts, PARP inhibitors, prognosis, and predictive biomarkers. To evaluate prognostic *BRCAness* biomarkers, we selected English-language articles in which HRD populations were treated or not. Publication types included original articles, review articles, and meta-analyses.

To evaluate the response to platinum salts and PARPi, we selected English-language publications in which the HRD population as predefined in part 2 was treated with platinum salts or PARPi. We focused on prospective randomized clinical trials and secondary retrospective data from prospective clinical trials; when no clinical data existed, we selected preclinical data.

3. Results

3.1. The HR pathway, BRCA1 and 2, and other genes implicated in the BRCAness phenotype

3.1.1. DNA damage, DNA damage repair, and the HR response (Table 1)

DNA damage repair is achieved by a set of complex signal events and enzyme activities from induction to detection of DNA damage that activate cell cycle checkpoints and repair DNA lesions by a variety of mechanisms. If DNA repair pathways are not functional and programmed cell death not triggered, DNA instability arises, which is a hallmark of cancer (Hanahan and Weinberg, 2011). To cope with DNA lesions, cells use at least five major repair pathways. To date, more than 450 proteins involved in different DDR pathways have been identified, transforming the concept of a linear and simplistic pathway into a dynamic overlapping of interconnected networks (Pearl et al., 2015).

3.1.1.1. Repair of DNA damage to one strand of DNA. Base excision repair (BER) and nucleotide excision repair (NER) are the two main pathways involved in the repair of damage on a single strand DNA.

3.1.1.1.1. BER. BER involves a multistep machinery that repairs small DNA lesions by removing non–helix-distorting base lesions (Brenerman et al., 2014). Among the many sensors involved in this pathway, PARP1 and PARP2 are responsible for catalyzing the ADP ribose unit into long, branched chains of poly ADP ribose. The binding of PARP distorts DNA, allowing for the localization of the proteins involved in the DDR, such as topoisomerases, DNA ligase III, DNA polymerase ß, and XRCC1 (Molinete et al., 1993).

3.1.1.1.2. NER. NER repairs bulky helix-distorting lesions with DNA adducts caused by UV light, ionizing radiation, or cross linking agents used in chemotherapy such as platinum salts. Damaged regions are removed in 12–24 nucleotide strands in two subpathways: global genome NER and transcription-coupled NER, depending on the cell cycle phase. These two subpathways share three steps – incision, repair, and ligation – and differ in protein sensors (Scharer, 2013).

3.1.1.1.3. Mismatch repair (MMR). The MMR pathway corrects replication errors producing double strand mismatches due to misincorporation of nucleotides or insertions/deletions. Defects in the MMR pathway increase spontaneous mutation rates and are associated with the hereditary Lynch syndrome (Jiricny, 2006).

3.1.1.2. DNA DSBs repair. DSBs occur when the two complementary strands of the double helix are simultaneously broken. The DSBs can be repaired by two competing processes HR or Non-Homologous End-Joining (NHEJ). But the initial steps of DSBs are common and involve

Table 1
The five DNA repair pathways and their associated linkage.

DNA damage	Single-strand break Base damage and modified base	Bulky DNA adducts Inter- and intrastrand crosslinks	Base mismatches Insertion and deletion loops	Double-strand break Interstrand crosslinks	Double-strand break
DNA repair pathway	BER	NER	MMR	In S-G2 phase = HR	In G0-G1 phase = NHEJ
Key molecules involved	XRCC1 PARP1 PARP2 POLβ	XPA, RPA, TFIIH, ERCC1	MSH2, MSH3, MSH6 MLH1, MLH3, PMS2	RAD50, RAD51, BRCA1, BRCA2, PALB2, TP53BP1, PARP1, PARP2 Indirectly: ATM, CHK1, CHK2, PTEN	53BP1, RIF1, Ku70, Ku80, LIG4, XRCC4, POLQ, DCLRE1C (Artemis), XRCC1, DNA-PKcs
Cancer linkage	MUTYH (MAP MUTYH associated polyposis)	Xeroderma pigmentosum Cockayne syndrome	HNPPC Lynch syndrome	BRCA1 or 2 mutations, NBS1 (Nijmegen breakage syndrome) ATM, BML, WRN, RAS54 and CtLp (lymphoma and leukemia),RAD51B (uterine leiomyoma), RECQL4 (skin cancer, osteosarcoma and BC) P53 (Li Fraumeni syndrome) PTEN (Cowden syndrome) CHK2 (breast, colorectal stomach, prostate, kidney, thyroid, sarcoma) PALB2 (breast and pancreas)	

BER = Base excision repair; NER = nucleotide excision repair; MMR = Mismatch repair; HR = homologous recombination; NHEJ = Non Homologous End-Joining.

activation of the checkpoint kinase ataxia telangiectasia-mutated (ATM), which is the most upstream actor in DNA damaging signaling (Hartlerode and Scully, 2009; Jacquemont and Taniguchi, 2007). ATM phosphorylates and activates numerous substrates, among which p53 and CHK2, which will signal downstream to block the cell cycle or activate apoptosis. Activation of either HR or NHEJ is dependent on the cell cycle phase. Indeed, the highly reliable HR uses the sister chromatid, which contains the missing genetic information, as a template and, thus, is activated during the S and G2 phases, when the genome is being duplicated. The rapid, but error prone, NHEJ that mends the two broken extremities on the basis of micro-homologies, is activated in G1 when sister chromatids are not available.

3.1.1.2.1. HR (Fig. 1). HR is a complex mechanism involving a profusion of proteins that interact in a very precisely choreographed sequence of interventions. A number of the principal actors are tumor suppressor and cancer predisposing genes such as ATM, BRCA1 and BRCA2, which recruit downstream actors and command the proper sequence of events. Interestingly, the *RAD51*, *BARD1*, *PALB2*, *BRIP1* and *NBN* genes, that code for downstream actors, are also the target of mutations in small subfractions of breast and ovarian cancer. BRCA1 is indispensable to the initiation of the process, as it displaces 53BP1 of the DSB sites, allowing the recruitment of CtIP and the MRN complex and resection of the loose DNA end. This step is essential to RAD51 binding, catalyzed by BRCA2. RAD51 forms homopolymers, which are indispensable to sister chromatid invasion and final recombination. The PARP1, known for its role in single strand gap protection and repair in the BER pathway, plays an important part in HR as well (Arnaudeau et al., 2001); (Bryant et al., 2009). Indeed, PARP1 poly-ADP-ribosylates and activates MRN and ultimately DNA end resection. Furthermore, it has been shown that PARP1 PARsylates and regulates *BRCA1* avoiding excessive HR and hyper-recombination, which lead to genetic instability (Hu et al., 2014).

3.1.1.2.2. NHEJ. NHEJ is a quick and error-prone repair pathway that ligates DSBs with minimal end processing. It is predominant during G0 and G1 cell cycle phases and considered to be responsible for the repair of up to 85% of IR-induced DSB. Initial steps of NHEJ involve binding of 53BP1, which protects DNA end from degradation by nucleases like MRE11 and recruits KU70 and KU80. KU70/80 displace 53BP1 and, together with DNA-PK, initiate end joining after recruitment of XRCC4 and DNA Ligase 4. Initial steps involve PARP1 in competition to 53BP1 and KU, which will recruit XRCC1 and LIG3 (De Vos and Schreiber, 2012).

3.1.2. Germline mutations affecting BRCA1/2 and other in DDR genes in human breast and ovarian carcinoma

While breast and ovarian cancer were respectively the second and the fifth leading causes of death in the United States in 2017 (Siegel et al., 2017), hereditary cancer accounts for less than 10% of BC (Balmaña et al., 2011) and 18–20% of epithelial ovarian carcinoma (EOC) (Walsh et al., 2011; Couch et al., 2017; Norquist et al., 2016) and is mostly linked to *BRCA1* or *BRCA2* gene mutations.

Approximately 80% of breast tumors developed in *BRCA1* mutation carriers display a triple-negative phenotype (characterized by a negativity for estrogen and progesterone receptors and human epidermal growth factor 2 receptor (*HER2*)) and/or a basal-like subtype upon gene expression profiling (Foulkes et al., 2003; Perou et al., 2000). In contrast, BC from *BRCA2* mutation carriers are frequently estrogen receptor (ER) positive and of the luminal BC subtype (Lakhani et al., 2005).

Likewise, EOC in patients with germline-mutated *BRCA1/2* are predominantly of the high grade serous type. There is no difference in histology or grade between *BRCA1* and *2* mutation carriers in EOC. One third of these patients will develop a BC before developing ovarian cancer (Mavaddat et al., 2012).

BRCA1 mutation carriers have a 65% (95% CI: 44–78%) cumulative lifetime risk for developing BC and 39% (95% CI: 18–54%) for developing EOC (Antoniou et al., 2003). Corresponding estimates for *BRCA2* mutation carriers are almost half that of *BRCA1* mutation carriers (Antoniou et al., 2003; Balmaña et al., 2011; Lee et al., 2014; Chen and Parmigiani, 2007). *BRCA1/2* mutation carriers have also a higher risk in both genders of developing pancreatic, stomach, head and neck cancer and in males prostate cancer (Balmaña et al., 2011). Other critical genes implicated in DDR, such as *PALB2*, have been associated with a genetic predisposition to breast and ovarian cancer and will be described later in this article.

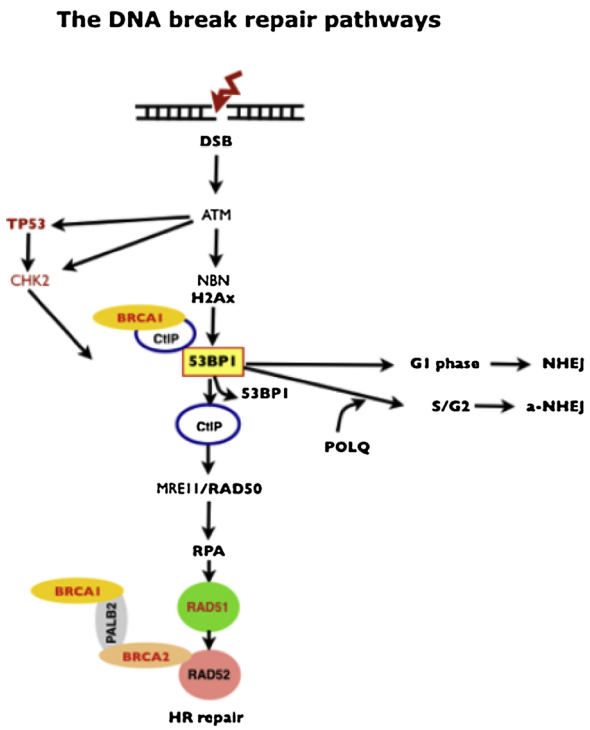

Fig. 1. DNA double-strand break repair by the homologous recombination repair pathway.

DNA double-strand break repair by the high-fidelity homologous recombination (HR) repair pathway during the G2 phase of the cell cycle. In response to DSBs, sensors detect the damage, and signaling mediators recruit or activate effectors that repair the damage.

In red are genes harboring germline and/or somatic inactivating mutations in epithelial ovarian cancer and breast cancer. DSB = double-strand break; CtIP = choline transporter like.

3.1.3. The BRCAness phenotype and associated dysfunctions in non-germline BRCA-mutated HR pathways

The *BRCAness* concept, introduced in 2004 by Ashworth et al. (Turner et al., 2004), is based on the identification of the hallmarks of germline *BRCA1/2* mutant carriers within sporadic breast and ovarian cancer. These authors speculated on "*the existence of a significant proportion of sporadic breast, ovarian, and other cancers with BRCA-like functional abnormalities raising the possibility of a wider application of treatment regimens designed for familial-BRCA tumors*" (Turner et al., 2004). Inactivating mutations of *BRCA1* and *BRCA2* genes are not frequent in sporadic breast and ovarian cancers. *BRCA1* can be silenced by epigenetic modification while other germinal and somatic mutations in genes involved in the HR pathway can be implicated. Abundant evidence underlines that these modifications reflect a common HR repair defect that could participate in the pathogenesis of a significant number of sporadic or familial non-germline *BRCA*-mutated cancers.

Aberrant methylation of the CpG island present at the *BRCA1* promoter has been reported in 11–14% of sporadic BC (Esteller et al., 2000; Rice et al., 2000), in 27–37% of triple-negative BCs (TNBCs) (Lips et al., 2013), and in 5–31% of ovarian cancers (Esteller et al., 2000; Geisler

et al., 2002; Catteau et al., 1999) *BRCA1* promoter methylation is almost always associated with reduction or loss of RNA and protein expression, because of the loss for the second allele through LOH (Baldwin et al., 2000; Chan et al., 2002). In contrast to *BRCA1*, no *BRCA2* promoter methylation is implicated in breast carcinogenesis and rarely so in ovarian cancer (Collins et al., 1997; Hilton et al., 2018). Instead, *BRCA2* expression has been proposed to be down-regulated by EMSY, a chromatin remodeling protein, shown to interact with the *BRCA2* transactivation domain and to repress its transcription. The *EMSY* gene is amplified and overexpressed in 13% BC and 17% HGSOC and this is considered as a manifestation of *BRCA2* inactivation in these tumors (Hughes-Davies et al., 2003).

Genes involved in the HR pathway, such as *PALB2, BRIP1, RAD50, RAD51, RAD51C and RAD54* have been reported to be mutated at low incidence in TNBC and ovarian cancer (Antoniou et al., 2014; Heikkinen et al., 2009; Pelttari et al., 2011; Loveday et al., 2012; Pelttari et al., 2012). Moreover, in TNBC, the overexpression of the meiosis gene *HORMAD1* has been shown to repress *RAD51* (Watkins et al., 2015). Dysfunction of the HR pathway also includes the promoter hypermethylation of genes involved in the HR pathway (*PALB2, ATM, RAD50, RAD51C, FANCF*) (Watanabe et al., 2013; Wang et al., 2006; Cunningham et al., 2014; Cancer Genome Atlas Research Network et al., 2011; Polak et al., 2017). The *PTEN* gene, which has been proposed to indirectly modulate *RAD51* expression, contribute to defective HR (Mendes-Pereira et al., 2009). Finally, deficiency in *ARID1A*, a chromatin-remodeling subunit of SWI/SNF, is responsible for impairing the DNA damage checkpoint and sensitizing cells to PARP inhibition in cell lines and animal models (Shen et al., 2015). In response to DNA damage, ARID1A is recruited to DSB *via* ATR to facilitate DNA DSB end resection. *ARID1A* is one of the most frequently mutated genes in human cancers and has been identified in BC, ovarian clear cell carcinoma (Jones et al., 2010), and endometrioid EOC (Wiegand et al., 2010).

MicroRNA (miRNA) also can contribute to *BRCAness*. MiRNAs are small endogenous noncoding RNAs of 20–27 nucleotides that negatively regulate gene expression at the post-transcriptional level by transcript destabilization or translational repression. Recent preliminary studies emphasize that BRCA mRNAs are a potential target of 20–100 miRNAs (Griffiths-Jones et al., 2008; John et al., 2004). Some miRNAs are identified as BRCA1 expression regulators within breast tumor cell lines (Moskwa et al., 2012) and HGSOC tumors (Liu et al., 2012) and have been correlated with PARP inhibition sensitivity (Moskwa et al., 2012).

The accumulation of germline and somatic mutations, as well as epigenetic inactivation of genes involved in HR has been estimated to affect up to 35% breast and 50% of ovarian cancers (Table 2 and above descriptions). HR defective cancers share elevated genomic instability, as well as *RB1* loss and high frequency of *TP53* mutation. These common characteristics suggest shared driving events and a common therapeutic opportunity (Cancer Genome Atlas Research Network et al., 2011; Cancer et al., 2012). However, optimal methods for evaluating this phenotype are needed.

3.2. Defining the HRD population: clinical, pathological, and biological tools

Defining more precisely the HRD population is one of the most important biological and clinical questions to date. However, identifying HRD tumors is challenging due to the larger number of potential genetic determinants. Various companion assays are currently being developed in parallel with PARPi development. Here, we discuss the accuracy of clinical, pathological, and biological tools to identify HRD tumors in the clinic.

3.2.1. Clinicopathological aspects

Clinical characteristics such as young age at onset, bilateral BC, or breast and ovarian cancer occurring in the same patient have been associated with *BRCA1/2* mutant carriers (Veronesi et al., 2005). *BRCA1/2* mutation frequency is low (1–7% for *BRCA1* and 1–3% for *BRCA2*) in unselected breast and ovarian cancers (Balmaña et al., 2011). Selection of patients based on familial history alone is limited in terms of positive predictive value (PPV) and negative predictive value (NPV). Studies testing cohorts have shown that 31–44% of women with a germline *BRCA* mutation do not report a significant family history of breast and ovarian cancer (Alsop et al., 2012; Daniels et al., 2014). Conversely, the mutation incidence of *BRCA1* in a group of BC with a familial history is low (25%) (Veronesi et al., 2005). Thus, selecting patients based on cancer history alone is not sufficient because of a substantial number of germline *BRCA1/2* tumors arising *de novo* and because of unidentified germline or somatic mutations affecting genes of the HR pathway.

BRCAness phenotype is essentially associated with high-grade TNBC with basal-like features (Atchley et al., 2008) and HGSOC. However, the PPV of hormonal receptor and HER2 negativity is unsatisfactory. A recent study screened for and identified deleterious mutations in 17 predisposition genes, mainly belonging to the HR pathway, in only 14% of TNBC patients unselected for familial cancer. The majority of deleterious mutations were identified in the *BRCA1* (8.5%), *BRCA2* (2.8%), and *PALB2* (1.2%) genes (Couch et al., 2017). Heterogeneity of TNBC biology might be an explanation for these results. TNBC tumors are mostly invasive carcinoma with no specific type (95%) and can include many other histopathologic subtypes such as medullary carcinoma, metaplastic carcinoma, adenoid cystic, adenosquamous carcinoma, and apocrine tumors. Medullary carcinoma appears overrepresented in *BRCA1* mutation carriers (10% *versus* 1% in sporadic breast cancer cases) (Eisinger et al., 1998). Heterogeneity of TNBC is also highlighted by recent gene expression studies (Lehmann et al., 2011), with the *BRCA1* gene-deficiency signature being associated with the basal-like-1 subgroup.

Moreover, the NPV of TN status is low for *BRCA2* mutant carriers because *BRCA2*-mutant BC frequently presents as ER-positive luminal cancer. In the CIMBA study, only 16% of breast tumors arising in *BRCA2* mutation carriers were TNBCs (Mavaddat et al., 2012).

Regarding EOC, their histopathologic features cannot be considered as sensitive or specific of *BRCAness*. Mucinous histology has a good NPV because it is not observed in *BRCA1/2* mutant carriers. The probability of detecting *BRCA1/2* germline or somatic mutations within an unselected EOC population is around 12%, especially EOC type 1, and is largely associated with HGSOC (20%) (Arts-De Jong et al., 2016). Histopathologic features associated with *BRCA1/2* mutation differ from sporadic EOC. In the CIMBA study (Mavaddat et al., 2012), among *BRCA1/2* mutation carriers HGSOC represented 67%, even if other rare histopathological subtypes, especially high-grade endometrioid cancers and clear cell carcinomas, were also described. Most recently, in the Pennington et al. Pennington et al. (2014) and Aghajanian et al. studies (Aghajanian et al., 2017), HR gene mutations (germline and somatic) were identified in the same proportion of serous and non-serous types in nearly all tested subtypes (Table 2).

Thus, a *BRCAness* phenotype suggested by clinical and histopathologic features lacks sensibility and specificity, leading to the search for new, reliable molecular assays to *identify* tumors affected by BRCAness.

BRCAness is defined by an exquisite sensitivity to DNA-crosslinking agents such as platinum salts and PARPi. *BRCA1/2* carriers with breast tumors have a higher response rate in the neoadjuvant setting (72–83% of pathologic complete response (pCR) rate) (Byrski et al., 2009; Byrski et al., 2010) and in the metastatic setting (around 68–80% of response) using platinum salts (Byrski et al., 2012; Tutt et al., 2018). Platinum salts are not typically used in BC treatment. However, considering the predictive value of *BRCA1/2* mutations, this regimen could be considered in the treatment *of BRCA1/2*–mutated TNBC or endocrine-resistant advanced/metastatic BC previously treated with a taxane and an anthracycline, as suggested by the recent ABC guidelines (Cardoso et al., 2014).

Table 2
Selected relevant studies regarding germline and somatic mutations in HRD in ovarian and breast cancer.

study	Histology subtype	Germline and somatic mutations in HRD genes
TCGA study (Cancer et al., 2012)	510 BC (93 basal; 57 HER2 enriched; 224 luminal A; 124 luminal B)	Germline mutation 9.7% (*BRCA1* 2.5%; *BRCA2* 2.6%; BRIP1 0.5%; *ATM* 1.5%; *CHEK2* 0.4%; *PTEN* 0.2%; *RAD51C* 0.2%; other 1.8%) Somatic mutation (*BRCA1* 1.4%; *BRCA2* 2%)
Nik-Zainal et al. (Nik-Zainal et al., 2016)	560 BC	Germline *BRCA1* and 2 mutations 10.7% Somatic *BRCA1* and 2 mutations 2.5%
Shah et al. (Shah et al., 2012)	65 TNBC	Somatic mutation BRCA2 3.1%; PTEN and RB1 7.7%
Pohl et al. (Pohl et al., 2017)	6507 BRCA1/2-negative germline mutated BC and EOC	Germline HRD mutation 5.8% *(CHEK2* 2.3%; *ATM* 1.4%; and *PALB2* 1.1%; RAD*51C* 0.3%; *TP53* 0.2%; *NBN* 0.2%; *CDH1* 0.2%; and *RAD51D* 0.1%)
TCGA study (Cancer Genome Atlas Research Network et al., 2011)	316 HGSOC	Germline mutations 17% (*BRCA1* 9%; *BRCA2* 8%) Somatic mutations 28% (*EMSY 8%; PTEN 7%; FANCA 5%; RAD51C 3%; BRCA1/2 3%; ATM 2%)*
Tuya et al. (Pal et al., 2005)	209 invasive ovarian carcinomas (121 serous; 13 mucinous; 29 endometrioid; 9 clear cell; 37 other)	15.3% germline *BRCA1/2* mutation (*BRCA1* 9.6%; *BRCA2* 5.7%)
Zhang et al. (Zhang et al., 2011)	1342 invasive ovarian carcinomas	13.3% germline *BRCA1/2* mutation (*BRCA1* 8.1%; BRCA2 5.1%; both *BRCA1* and *2* 0.1%)
BROCA study (Pennington et al., 2014)	390 ovarian, fallopian tube, and peritoneal carcinoma (249 HGSOC; 9 LGSOC; 48 poorly differentiated NOS; 19 clear cell; 20 high-grade endometrioid; 6 low-grade endometrioid; 12 carcinosarcoma; other 4)	Germline HRD mutation 24% (*BRCA1* 13.4%; *BRCA2* 4.6%; in other HR genes 6%) Somatic HRD mutations 8.7% (*BRCA1* 4.7%; *BRCA2* 1.5%; *ATM* 0.8%; *BRIP1* 0.2%; *CHEK2* 0.8%; *MRE11A* 0.3%; *RAD51C* 0.3%)
Walsh et al. (Walsh et al., 2011)	360 women undergoing primary surgery (273 ovarian carcinoma; 48 peritoneal carcinoma; 31 fallopian tube carcinoma; 8 endometrial and ovarian carcinomas)	Germline HRD mutation: *BRCA1* 11.1%; *BRCA2* 6.4%; in 10 other genes 6.1% (*BARD1*, *BRIP1*, *CHEK2*, *MRE11*, *MSH6*, *NBN*, *PALB2*, *RAD50*, *RAD51C*, *TP53*)
Norquist et al. (Norquist et al., 2016)	1915 women with EOC (1498 HGSOC; 70 LGSOC; 165 poorly differentiated NOS; 58 clear cell; 64 high-grade endometrioid; 13 low-grade endometrioid; 22 carcinosarcoma; mucinous 16; transitional cell 9)	Germline HRD mutation 18% : *BRCA1* 9.5 %; *BRCA2* 5.1%; in other HR genes 3.26% (*BARD1 0.2%*, *BRIP1 1.3%*, *PALB2 0.62%*, *RAD51C 0.57%*, *RAD51D 0.57%*)
Aghajanian et al. (Aghajanian et al., 2017)	260 EOC (60% HGSOC; 13% LGSOC; 13% clear cell; 4% mucinous; 3% endometrioid; 7% mixed/other histology)	Somatic HRD mutations 18% (*BRCA1* 4%; *BRCA2* 2.7%; *ATM* 1.9%; *BARD1* 1.6%; *BRIP1* 0.4%; *CHEK1* 0.4%; *CHEK2* 0.4%; *FANCA* 0.8%; *MRE11* 1.6%; *PTEN* 5%)

BC = breast cancer; EOC = epithelial ovarian cancer; HGSOC = high grade serous ovarian cancer; LGSOC = low grade serous ovarian cancer; TNBC = triple negative breast cancer; HRD = homologous recombination deficiency, NOS = Not otherwise specified.

Concerning EOC, platinum salts are the classical backbone of the treatment in first-line therapy. The second-line therapy is stratified on the platinum-free interval and the platinum sensitivity of the tumor. EOCs in *BRCA1/2* carriers are characterized by a higher response rate and prolonged progression-free survival (PFS) after platinum-based therapy, compared with non-mutated *BRCA1/2* patients. In the Alsop et al. study, an enrichment of somatic *BRCA* mutations was described among patients without germline mutations who responded repeatedly to treatment with platinum salts (Alsop et al., 2012). Platinum salt response in EOC should be a good positive predictive marker of PARPi response. The study by Gelmon et al. lead to clear conclusions on this topic, as they observed, in a cohort of platinum-sensitive EOC, a 50% objective response rate with olaparib in the *BRCA1/2* wild-type cohort compared to 13% in the platinum-resistant cohort (33% in *BRCA1/2* mutated cohort and only 4% in BRCA1/2 negative cohort) (Gelmon et al., 2011). These findings laid the basis of the current development of the PARPi olaparib (study 19 (Ledermann et al., 2012) and SOLO2 (Pujade-Lauraine et al., 2017), rucaparib (ARIEL3 (Coleman et al., 2017) and niraparib (NOVA trial (Mirza et al., 2016) as a maintenance therapy in platinum sensitive EOC. However, about 15% of the *BRCA1/2* germline mutated EOC progress within 6 months after completing primary-based chemotherapy and are classified as platinum resistant. In this population with platinum-resistant *BRCA*-mutated EOC, a 33% response rate to olaparib was reported (Gelmon et al., 2011). Thus, defining a *BRCAness* group is still of interest to predict tumor behavior and response to platinum salts and PARPi. In addition, waiting for the evaluation of drug response to define the *BRCAness* phenotype is not useful in clinical practice for first-line treatment decisions and is not relevant especially for TNBC.

3.2.2. Germline BRCA1/2 mutations

Thousands of different *BRCA1/2* mutations have been identified. They are not equivalent in terms of average and magnitude risk for breast or ovarian cancer (Labidi-Galy et al., 2018; Rebbeck et al., 2015) Moreover, the average risk associated with many of the sequence variants remains unclear, and these have been designated as “variants of unknown significance.” In the WECARE study, variants of unknown significance represented 75% of mutations detected, with some of these mutations conferring a biochemical difference that still could not be classified in terms of pathogenic implication (Borg et al., 2011). Thus, *BRCA1/2* analysis alone is not a reliable and global method for identifying *BRCAness* is mandatory.

3.2.3. Promoter methylation in HRD genes

As previously discussed, one third of HRD breast cancers are associated with *BRCA1* promoter hypermethylation (Schouten et al., 2015). Evaluation of this feature appears highly relevant, in conjunction with the germline and somatic mutation status, to avoid underestimation of the *BRCAness* population. The histopathologic and molecular characteristics of BC with *BRCA1* promoter hypermethylation are similar to those of BC with *BRCA1* germline mutation (Kawazu et al., 2017): higher histologic grade and a mostly TNBC and basal-like BC profile with a striking association with medullary and mucinous subtypes (Zhu et al., 2015; Esteller et al., 2000; Catteau et al., 1999). Concerning EOC, *BRCA1*-methylated tumors are more likely to be HGSOC compared to non-methylated and non-mutated tumors (Sun et al., 2017), with a similar frequency compared to *BRCA1* germline-mutated tumors (Cancer Genome Atlas Research Network et al., 2011). *BRCA1* promoter methylation and *BRCA1/2* mutation are considered mutually exclusive (Lips et al., 2013; Cancer Genome Atlas Research Network et al., 2011; Sun et al., 2017; Yang et al., 2011), although some rare cases of coexistence have been described (Vos et al., 2017). Other epigenetic defects in HR genes have been described (*e.g.*, *RAD51C* (Cancer Genome Atlas Research Network et al., 2011; Cunningham et al., 2014; Polak et al., 2017) and *FANCF* promoter methylations (Wang et al., 2006) in the EOC population and need to be evaluated.

3.2.4. Germline and somatic mutations in HRD genes

Several studies reported HRD-associated germline and somatic mutations in ovarian and BC (Table 2). The BROCA study screened a panel of 21 tumor suppressor genes for germline and somatic mutations. These included *BRCA1/2* and 11 genes of HRD pathway (*PALB2, BARD1, BRIP1,* CHEK2*, MRE11 A, MSH6, NBN, PALB2, RAD50, RAD51C*, and *TP53*) (Pennington et al., 2014) in 390 ovarian or peritoneal or fallopian tube carcinomas. These authors found that the majority of germline and somatic HRD gene abnormalities were located in the *BRCA1/2* genes, while mutations in the non-*BRCA* HRD genes represented 26% of the mutations. A similar mutation frequency was described in patients with non-HGSOC, including clear cell carcinoma, high-grade endometrioid carcinoma, and carcinosarcoma but with a different spectrum of target genes. These results are in concordance with those reported by the TCGA project performed in 316 HGSOCs that reported a total incidence of 50% of HR defects in HGSOC. However, the analysis included more genomic alterations compared to the BROCA study, including *BRCA1* hypermethylation (11%), *EMSY* amplification or mutation (8%), and *RAD51* hypermethylation (3%) (Cancer Genome Atlas Research Network et al., 2011). A better understanding of how mutations interact to affect DDR may be necessary to predict response and resistance to drugs targeting parallel repair pathways.

3.2.5. Genetic signatures

Because numerous mechanisms lead to HRD, it could be interesting to define the *BRCAness* phenotype by means of a gene expression profile associated with the germline *BRCA1/2* mutant phenotype.

3.2.5.1. mRNA and miRNA signatures. Konstantinopoulos et al. developed an EOC *BRCAness* gene expression profile, allowing identification of three groups encompassing the *BRCA1, BRCA2*, and sporadic clusters respectively. These authors then used these clusters to generate a 60-gene predictor that could distinguish the BRCA-associated cluster from the sporadic cluster (Konstantinopoulos et al., 2010). Other assays have been developed in small series, with no consistent results. These studies presented limitations being retrospective and based on small patient numbers and did not take other prognostic biomarkers into account (Egawa et al., 2003; Wysham et al., 2012; Dann et al., 2012).

3.2.5.2. Mutator phenotype. Undermining the mechanisms that preserve genome integrity leads to genomic instability and the acquisition of a mutator phenotype. Defining this phenotype can allow for selection of treatment that targets this instability. Many assays have been developed to define subclasses of genomic instability to be proposed as companion assays for clinical practice. Recent work by Davies et al. (2017) proposed to identify HR defective tumors on the basis of genome-wide mutation signatures that specified deficiencies in DNA repair pathway (Davies et al., 2017). Although this approach appeared promising, it may not enter clinical practice easily, being based on whole genome sequencing.

3.2.5.2.1. DNA copy number alteration (CNA) profiles. DNA CNA is defined as a gain or loss of DNA content in tissue. A phenotype with high CNA is associated with genome instability defined as a characteristic of BRCA-deficient tumors. Joose et al. built a classification based on a comparative genomic hybridization array (aCGH) profiles of *BRCA1*-related and control BCs with the aim to differentiate *BRCA1*-mutated from sporadic BCs (Joosse et al., 2009). They demonstrated a high sensitivity (88%) and a high specificity (94%) to identify *BRCA1*-mutated tumors in independent validation sets. Only 2 of 48 non–*BRCA1*-mutated tumors were characterized by a BRCA1-like CGH pattern, possibly because of other *BRCAness* phenotype mechanisms, such as promoter hypermethylation (Joosse et al., 2009). A *BRCA2*-like CGH pattern has also been described (Lips et al., 2011a).

Using single nucleotide polymorphism (SNP), different signatures were elaborated through comparison of *BRCA1/2* mutated and non-

mutated tumors. Von Waldhe et al. recently demonstrated concordance between HRD scores across different regions of the same tumor, indicating that HRD affects the entire primary tumor and corresponds to a founding event (von et al., 2017). Several teams independently identified an aberrant chromosomal rearrangement signature that was the result of HRD.

3.2.5.2.1.1. HRD - LOH score

A specific pattern of LOH results in irreversible loss of one of the parental alleles (Abkevich et al., 2012). An HRD–LOH score was developed by Abkevitch et al. from Myriad Genetics Inc (Utah, USA). The LOH score is defined as the number of subchromosomal segments with LOH affecting 15 Mbp. This HRD score was strongly correlated with functional defects in *BRCA1/2* and with promoter methylation of *RAD51* (Abkevich et al., 2012).

Using a different LOH profile they developed, Wang et al. stratified HGSOC into a LOH-high and a LOH-low group. Interestingly, a similar stratification LOH-high *vs.* LOH-low could be applied to TNBC, but not to HER2-positive and ER + high-grade BC. This observation further favored the concept of a shared HR-deficiency in HGSOC and TNBC (Wang et al., 2012).

3.2.5.2.1.2. HRD - telomeric allelic imbalance (HRD-TAI)

Allelic imbalance is defined as the unequal contribution of paternal and maternal DNA sequences with or without changes in overall DNA copy number. Birkbak et al. developed the telomeric allelic imbalance (TAI) score, which calculates the allelic loss extending from the site of DNA damage to the telomere (Birkbak et al., 2012). They demonstrated an inverse relationship between a low level of *BRCA1* mRNA and this score in sporadic TNBC and HGSOC without *BRCA1/2* mutation.

3.2.5.2.1.3. HRD - large scale transition (HRD-LST)

Large-scale transitions (LSTs) are defined as chromosomal breaks (translocations, inversions, or deletions) of at least 10 Mb between adjacent regions. The LST number has been evaluated for each chromosome arm independently allowing for ploidy status and appeared to be another robust signature for *BRCA1/2* inactivation in basal-like BC. Measure of LST and its cutoff to determine *BRCA1* status was validated in a second independent series of basal-like BC and basal-like breast cell lines with 100% sensitivity and 90% specificity (Popova et al., 2012).

3.2.5.2.1.4. Composite scores

Considering the various opportunities to evaluate HRD, it was tempting to combine different methods to dispose of a wider assay to identify HRD tumors and thus reduce the percentage of missed *BRCAness* detection. A composite score was recently developed by Foundation Medecine. These HR scores used two combined measures: *BRCA1/2* mutational status and percentage of LOH. According to this test, patients with relapsed, platinum-sensitive HGSOC are assessed for three groups: *BRCA* mutant (deleterious germline or somatic), *BRCA* wild type and LOH high score, or BRCA wild type and LOH low score (Swisher et al., 2016).

The MyChoice HRD test is another composite score developed by Myriad Genetics Inc (Utah, USA). It is based on three combined measures to formulate an HRD score: LOH, TAI, and LST. The scores are highly correlated with each other and with the presence of a *BRCA 1/2* defect (defined as *BRCA1/2* mutation or *BRCA1* promoter methylation and loss of the second allele of the affected gene). Its sensitivity to detect *BRCA1/2* deficiency in a breast cancer cohort was enhanced regardless of the cancer subtype (Timms et al., 2014). In Telli et al., the HRD score and cut-off threshold were elaborated using a training set of 497 breast and 561 chemotherapy-naive ovarian cancers with known *BRCA1/2* status. A threshold HRD score ≥ 42 allowed for identification of all but one *BRCA1/2*-mutated tumors (96.3%) in three neoadjuvant TNBC trials of platinum-containing regimens (Melinda et al., 2016).

3.2.5.2.2. Multiplex ligation-dependent probe amplification (MLPA) assay. Because CGH array is not carried out easily in clinical practice, this *BRCA*-like pattern was translated to the MLPA assay that targets the most specific *BRCA1*-associated genomic region. The BRCA1-like MLPA profile classification was designed to identify *BRCA1*-mutated BC and a *BRCA1* genomic-like profile within sporadic tumors. MLPA classification is highly correlated with the CGH-based *BRCA1*-like classification (6% of the overall error rate) (Lips et al., 2011b). In a blinded MLPA validation study, the MLPA assay predicted 83% of a sample with a *BRCA1* mutation and 91% of sample with *BRCA* promoter methylation within an independent cohort of 144 TNBCs (Gross et al., 2016).

3.2.6. Functional ex vivo assays

These assays are based on the evaluation of *RAD51* functionality, a major effector of the HR pathway, using immunofluorescence after exposure of tumor cells to DNA-damaging agents such as radiation (Naipal et al., 2014; Mutter et al., 2017). This test can be performed only on fresh, viable tissues after exposure to DNA damage, which is difficult to achieve in routine clinical practice (Mukhopadhyay et al., 2012).

However, the multiplicity of assays proposed to identify *BRCAness*, in absence of standardized well-conducted comparison of these methodologies, does not allow defining a gold standard assay for a reliable identification of HRD tumors.

3.3. Clinical need for BRCAness validated biomarkers in TNBC and HGSOC

Considering the poor prognosis of TNBC and HGSOC as well as the scarcity of therapeutic agents in this situation, identifying HRD tumors may allow for better patient stratification and clinical care improvement of these patients. Several clinical studies have been recently published that sought to identify HRD in TNBC and HGSOC and to establish its clinical impact, allowing for identification of a population that would benefit from HRD-targeting agents.

3.3.1. Prognostic value

Table 3 summarizes the current data regarding the prognostic value of HRD classifiers. The prognostic value of germline *BRCA1/2* mutation in BC is unclear. Few studies have compared overall outcome in BC patients with *BRCA1/2* germline mutations, with *BRCA1/2* wild type patients, and results were mixed (Cortesi et al., 2010; Musolino et al., 2007; Bordeleau et al., 2010; Copson et al., 2018). Systematic review and meta-analysis of 60 studies found that among patients diagnosed with TNBC, *BRCA1/2* mutation carriers had a better outcome compared to patients with wild-type *BRCA1/2* (hazard ratio, 0.49; 95% CI: 0.26–0.92; $p = 0.03$) (Baretta et al., 2016). Recently, the POSH study, a prospective cohort study of young women at first diagnostic of invasive BC, showed no difference in survival between patient carrying *BRCA1/2* mutation and patient carrying no mutation. However, in the TNBC subgroup, *BRCA1/2* carriers had a better overall survival (OS) than non-carriers (Copson et al., 2018). This advantage in this subgroup could be explained by a better chemosensitivity of *BRCA1/2* mutant BC. Since not all BC received chemotherapy, while a vast majority of TNBC patients did, this could introduce a bias to evaluate the prognosis value. This is not the case in EOC since virtually all patients receive platinum base chemotherapy. In a recent meta-analysis, EOC displaying germinal *BRCA1*/2 mutations had improved OS compared with non-mutated EOC (hazard ratio, 0.67; 95% CI: 0.57–0.78; $p < 0.001$) (Xu et al., 2016; Sun et al., 2014).

Evidence suggests that *BRCA1/2* somatic mutations in ovarian cancer lead to improved outcomes compared to wild-type tumors (Hennessy et al., 2010; Pennington et al., 2014). Likewise, the *BRCAness* phenotype as determined by gene expression profiling is associated with improved outcome compared with non-*BRCAness* in EOC (Konstantinopoulos et al., 2010). A high HRD score, as well as identification of genomic scars, has been correlated with better survival (Abkevich et al., 2012).

Several small studies have found that the prognostic significance of *BRCA1* promoter methylation is lower compared to somatic or germline mutations (Cancer Genome Atlas Research Network et al., 2011; Chiang

Table 3
BRCAness markers as prognostic and predictive biomarkers in TNBC and HGSOC.

	Indication HR deficiency	Dataset used	Indicating prognosis	Dataset used	Study	Indicating drug sensitivity	Dataset used	Study
Mutation	BRCA1/2 germline BRCA1/2 somatic mutation		Favorable (Sun et al., 2014; Xu et al., 2016) Unfavorable (Baretta et al., 2016) Favorable (Copson et al., 2018) Favorable (Hennessy et al., 2010; Pennington et al., 2014)	EOC (Sun et al., 2014; Xu et al., 2016) Overall BC (Baretta et al., 2016) TNBC (Copson et al., 2018) 235 EOC (Hennessy et al., 2010)	Meta-analysis of 35 studies (Sun et al., 2014) Meta-analysis of 60 studies (Baretta et al., 2016) Retrospective from prospective study (Copson et al., 2018)	Yes (carboplatin) (Tutt et al., 2018) Yes (olaparib) (Armstrong et al., 2017) Yes (talazoparib) (Litton et al., 2017 YES (olaparib) (Ledermann et al., 2012) Yes (niraparib) (Mirza et al., 2016) Yes (rucaparib)(Coleman et al., 2017)	376 metastatic TNBC (Tutt et al., 2018) 302 germline BRCA1/2-mutated metastatic HER2-negative BC (Armstrong et al., 2017) 431 germline BRCA1/2-mutated metastatic HER2-negative BC (Litton et al., 2017) 265 relapse BRCA1/2 germline- or somatic-mutated EOC carboplatin sensitive (Ledermann et al., 2012) 203 relapse BRCA1/2 germline-mutated EOC carboplatin sensitive (Mirza et al., 2016) 564 Relapse EOC carboplatin sensitive with 196 BRCA1/2 germline or somatic mutated carriers (Coleman et al., 2017)	Prospective randomized phase 3 trial (control arm = docetaxel (Tutt et al., 2018) Prospective randomized phase 3 trial (control arm = standard of care chemotherapy) (Armstrong et al., 2017) Prospective randomized phase 3 trial (control arm = standard of care chemotherapy (Litton et al., 2017) Randomize phase II clinical trial (control arm = placebo) (BRCA status pre planned study) (Ledermann et al., 2012) Double-blind phase 3 study with a control arm (placebo) stratified according germline mutation of BRCA (Mirza et al., 2016) Double-blind phase 3 study with a control arm (placebo) stratified according germline mutation of BRCA (Coleman et al., 2017)
Methylation promoter BRCA1	Methylation-specific PCR assay		Debate (Sun et al., 2014) Unfavorable (Wu et al., 2013)	EOC (Sun et al., 2014) 3205 BC (Wu et al., 2013)	Meta-analysis of 35 studies (Sun et al., 2014) Meta-analysis of 9 studies with BC (Wu et al., 2013)	No (carboplatin) (Tutt et al., 2018) Yes (cisplatin and carboplatin) (Teodoridis et al., 2005) Yes (rucaparib) (Swisher et al., 2016)	376 metastatic TNBC (Tutt et al., 2018) 106 stage III and IV EOC (Teodoridis et al., 2005) EOC platinum sensitive (Swisher et al., 2016)	Prospective randomized phase 3 trial (control arm = docetaxel (Tutt et al., 2018) Retrospective study with no control arm (Teodoridis et al., 2005) Phase 2 trial (Ariel 2) not randomized and no control arm (Swisher et al., 2016)
NGS	30 genes associated with HDR phenotype (Pennington et al., 2014)		Favorable (Pennington et al., 2014)	243 EOC	Retrospective study with a control arm (no germline or somatic HR gene mutations) (Telli et al., 2015)	Yes (platinum sensitivity) (Pennington et al., 2014)	243 EOC (Pennington et al., 2014)	Retrospective study with a control arm (no germline or somatic HR gene mutations) (Pennington et al., 2014)

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Table 3 (*continued*)

	Indication HR deficiency	Dataset used	Indicating prognosis	Dataset used	Study	Indicating drug sensitivity	Dataset used	Study
mRNA and miRNA signature	60 gene signature (Konstantinopoulos et al., 2010) DNA repair deficiency signatures (BRCAness and PARPi-7 composition)	61 sporadic and BRCA-mutated EOC (Konstantinopoulos et al., 2010)	Favorable (Konstantinopoulos et al., 2010)	70 EOC (Konstantinopoulos et al., 2010)	Retrospective study (Konstantinopoulos et al., 2010)	Yes (Konstantinopoulos et al., 2010) Yes (PARP inhibitors) (Konstantinopoulos et al., 2010) Yes (neoadjuvant veliparib with carboplatin with chemotherapy) (Wolf et al., 2017)	10 biopsies from 6 BRCAm patients (Konstantinopoulos et al., 2010) 12 clones of BRCA2 mutated pancreatic cell line (Capan-1) (Konstantinopoulos et al., 2010) 115 HER2- stage II and III BC (Wolf et al., 2017)	Preclinical trial (Konstantinopoulos et al., 2015) Preclinical data (Konstantinopoulos et al., 2010) Retrospective study from a prospective randomized I-SPY-2 trial (abstract P3-06) controlled trial (Wolf et al., 2017)
DNA copy number variation by CGH	BRCA1-like aCGH profile (Joosse et al., 2009) BRCA2-like CGH profile (Lips et al., 2011a)	82 BRCA and sporadic BC (Joosse et al., 2009) ER + /HER2- BC (Lips et al., 2011a)				Yes (adjuvant carboplatin includes in HD-CT) within BRCA-like CGH profile (Vollebergh et al., 2011; Vollebergh et al., 2014) Yes (adjuvant carboplatin included in HD-CT within BRCA-like CGH profile) (Schouten et al., 2015)	230 and 249 stage III HER2-negative BC (Vollebergh et al., 2011; Vollebergh et al., 2014) 117 high-risk stage II and III BC (Schouten et al., 2015)	Retrospective study from a prospective randomized controlled trial, adjuvant setting (Rodenhuis et al., 2003) Retrospective study for a single institution cohort Not randomized, adjuvant setting (Schouten et al., 2015)
MLPA assay	BRCA1 like MLPA profile (Lips et al., 2011b)	39 BRCA 1–like a CGH BC and 45 non–BRCA1-like a CGH BC (Lips et al., 2011b)				Yes (adjuvant carboplatin includes in HD-CT) (Lips et al., 2011b)	46 TNBC (Lips et al., 2011b)	Exploratory study; retrospective tumors selected from prospective randomized controlled trial (Rodenhuis et al., 2003)
High HRD-LOH score	Indicate BRCA1/2 mutation and BRCA and RAD51 methylation (Abkevich et al., 2012)	2 independent EOC dataset (Abkevich et al., 2012)	Favorable (Abkevitch et al., 2012)	507 serous EOC (Abkevich et al., 2012)		Yes (neoadjuvant carboplatin gemcitabine, iniparib) (Telli et al., 2015)	93 early TNBC or germline BRCA-mutated BC (Telli et al., 2015)	Retrospective study from a prospective phase II trial, no control arm (Telli et al., 2015)
High Wang LOH score	Indicate BRCA deficiency (Wang et al., 2012)	47 HGSOC and 50 BC (Wang et al., 2012)	Favorable (Wang et al., 2012)	47 HGSOC	Retrospective study Control arm = low LOH score (Wang et al., 2012)	Yes (platinum salts) (Wang et al., 2012)	47 HGSG (Wang et al., 2012)	Retrospective study Control arm = HGSC with a low LOH score (Wang et al., 2012)
High HRD–TAI score	Indicative Low level of BRCAm RNA (Birkbak et al., 2012)	79 TNBC (Birkbak et al., 2012)				Yes (neoadjuvant cisplatin-based chemotherapy) (Birkbak et al., 2012)	79 TNBC + a TCGA cohort of HGSC (Birkbak et al., 2012)	Retrospective from prospective study (cisplatin1-TNBC trial and cisplatin2-TNBC trial) (Silver et al., 2010)
High HRD–LST score	Indicating BRCA1/2 deficiency (Popova et al., 2012; Manié et al., 2016)	80 basal-like BC (Popova et al., 2012 and luminal BC Manié et al., 2016)				Yes (neoadjuvant cisplatin) (Manié et al., 2016)	Basal-like BC (Manié et al., 2016)	Exploratory analysis from prospective study (cisplatin1-TNBC trial and cisplatin2-TNBC trial) (Manié et al., 2016)
High HRD–LOH score + mutational BRCA1/2 status						Yes (rucaparib) (Coleman et al., 2017)	564 platinum-sensitive EOC	Double-blind phase 3 study with a control arm (placebo) stratified according germline mutation of BRCA and HRD-LOH score (Coleman et al., 2017)

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Table 3 (*continued*)

	Indication HR deficiency	Dataset used	Indicating prognosis	Dataset used	Study	Indicating drug sensitivity	Dataset used	Study
HRD test (HDR–LOH, HRD–LST)						Yes (carboplatin or cisplatin) (Isakoff et al., 2015)	86 metastatic TNBC (Isakoff et al., 2015)	Exploratory analysis from prospective phase 2 TBCRC009 trial, single arm (Isakoff et al., 2015)
MyChoice HRD test (HRD–LOH, HRD–TAI, HRD–LST)	Indicating BRCA1 promoter methylation, BRCA ½ mutation)	215 BC (Timms et al, 2014)				Yes (carboplatin and cisplatin)(Melinda et al., 2016) Yes (neoadjuvant carboplatin or cisplatin associated with various regimens) (Von Minckwitz et al., 2015) No (carboplatin) (Tutt et al., 2018) yes (niraparib) (Mirza et al., 2016)	200 stage I to III TNBC and/or *BRCAm* BC (Melinda et al., 2016) 267 TNBC or *BRCA* ½ m tumors (Von Minckwitz et al., 2015) 376 patients with metastatic TNBC (Tutt et al., 2018) 553 platinum-sensitive EOC (Mirza et al., 2016)	Single arm of three phase II studies: PrECOG 0105, Cisplatin-1, and Cisplatin 2 study (Melinda et al., 2016) Retrospective from prospective phase II trial (Von Minckwitz et al., 2015) Prospective randomized phase 3 trial (control arm = docetaxel (Tutt et al., 2018) Double-blind phase 3 study with a control arm (placebo) stratified according to germline mutation of BRCA (Mirza et al., 2016)
HR deficiency score: high HRD score (a combination of HRD–LOH, HRD–TAI, HRD–LST) or BRCAm						Yes (paclitaxel liposomal and carboplatin) (Von Minckwitz et al., 2014)	193 Stage II and III TNBC (Von Minckwitz et al., 2014)	Retrospective from a prospective randomized phase II trial (Von Minckwitz et al., 2014)
Functional test	Immunofluorescence-based assay (Mukhopadhyay et al., 2012)		Favorable (Mukhopadhyay et al., 2012)	50 EOC (Mukhopadhyay et al., 2012)	Prospective non-randomized study (Mukhopadhyay et al., 2012)	Yes (platinum) (Mukhopadhyay et al., 2012) Yes (rucaparib) (Mukhopadhyay et al., 2012)	50 EOC (Mukhopadhyay et al., 2012) Culture of ascitic fluid EOC and non-EOC (Mukhopadhyay et al., 2012)	Prospective non-randomized study (Mukhopadhyay et al., 2012)

BC = breast cancer; EOC = epithelial ovarian cancer; HGSOC = high-grade serous ovarian cancer; BRCAm = BRCA mutated; HRD = homologous recombination deficiency; HDR–LOH = homologous recombination deficiency–loss of heterozygosity score; HRD–TAI = homologous recombination deficiency–telomeric allelic imbalance; HRD–LST = homologous recombination deficiency–large-scale transition; TNBC = triple-negative breast cancer.

et al., 2006; Sun et al., 2014; Pennington et al., 2014; Xu et al., 2009). However, two meta-analyses showed that *BRCA1* promoter methylation was associated with unfavorable outcome compared to *BRCA1* promoter unmethylated BC (Wu et al., 2013; Zhang and Long, 2015). These conflicting observations may be explained by the heterogeneous inclusion criteria and study design (percentage of treated patients, treatment protocols) of the studies analyzed in this work.

The prognostic value of BRCA status should be balanced with its predicted drug response, and the improved outcome in carriers of *BRCA* mutations among EOC and TNBC cases might be explained by increased chemosensitivity.

3.3.2. Predictive biomarkers for chemotherapy and targeted therapy responses

According to ASCO recommendations on selecting a useful predictive biomarker for therapeutic management, a biomarker should have a strong analytic and clinical validity, and utility to define its level of evidence (LOE), as first proposed by the American Society of Clinical Oncology Tumor Markers Guidelines Committee (Hayes et al., 1996), and subsequently refined by the recommendations by Simon and colleagues (Simon et al., 2009). Schematically, according to methodological criterias, grade I LOE correspond to the highest LOE (based on dedicated prospective study) and grade III the lesser one, requiring additional studies before considering the possible use of the biomarker in clinical practice (Van Poznak et al., 2015; Simon et al., 2009).

3.3.2.1. Predictive biomarker for platinum salt response. Platinum salts are not particularly active in unselected BC mainly because of the low response rate of ER-positive BC (Decatris et al., 2004). However, TNBC appear particularly responsive to platinum-based regimen, as observed in a neoadjuvant randomized trials comparing the addition of platinum salts to that of a classical anthracycline/taxane combination (pCR rates 53% *vs.* 36%; 60% *vs.* 44%) (Von Minckwitz et al., 2014; Sikov et al., 2015). In the metastatic setting, although randomized trials suggested that TNBC patients show significant response to platinum salts (Mo, 2012), this does not exceed that of taxanes in an unselected population and has no survival impact. However, in the randomized Triple Negative breast cancer Trial (TNT) trial, germline *BRCA1/2* mutant carriers experienced significantly more benefit from carboplatin, with higher response rates (68% *versus* 33% p = 0.03) and longer PFS (6.8 *versus* 4.4 months) compared to docetaxel (Tutt et al., 2018). Nevertheless, in the GeparSixto trial testing the addition of carboplatin in a non-standardized neoadjuvant chemotherapy regimen (low dose of doxorubicin, and no cyclophosphamide) in TNBC, addition of carboplatin failed to improve pCR and DFS in germline mutation carriers. The use of two DNA-damaging compounds doxorubicin and carboplatin promoting the formation of DSB could be an explanation to these results (Hahnen et al., 2018). Moreover all germline *BRCA1* mutation variants are not equal in predicting platinum sensitivity. Different *BRCA1/2* mutations respond differently to platinum salt. BC with *BRCA1* mutation resulting in a RING-less BRCA1 protein were associated with resistance to platinum salts, caused by a residual activity of the mutant BRCA1 protein (Drost et al., 2011; Drost et al., 2016). For example, the *BRCA185delAG*, a common germline mutation in the Jewish Ashkenazi population, results in a RING-less BRCA1 protein that directly mediates cisplatin and PARPi resistance (Powell, 2016). Furthermore EOC with *BRCA2* mutation located in the RAD51 binding domain had a better PFS, OS and platinum free interval than non-carriers, while *BRCA2* carriers with mutations in other domains didn't show a better PFS or OS compared with non-carriers. The hypothesis behind these findings is that mutation in *RAD51* binding domain impair the ability to BRCA2 to recruit RAD51 to DSB involving a deficient HR (Labidi-Galy et al., 2018).

Clinical results with *BRCA1* promoter methylation were mixed, as they were associated with improved platinum response in stage III/IV EOC (Teodoridis et al., 2005), while this was not the case in metastatic TNBC (Tutt et al., 2018). This may be explained by changes of *BRCA1* methylation status over time related to clonal selection and treatment pressure (Baylin and Bestor, 2002; Kawazu et al., 2017).

Along the same lines, ovarian fallopian tube and peritoneal carcinomas (Pennington et al., 2014) and EOC with germline-inactivating mutations affecting key HR genes showed increased platinum sensitivity and prolonged OS (Walsh et al., 2011; Norquist et al., 2016). HRD mutations were identified in 307 patients (25.7%) from the population included in the GOG-0218 study, a large phase III trial assessing the impact of HRD gene on clinical outcome in women with EOC treated with platinum therapy. Women with *BRCA1/2* mutation and *non-BRCA* HRD mutations were affected by a better PFS and OS compared with those without mutations [hazard ratio, 0.73; 95% CI: 0.57–0.94 for PFS; hazard ratio 0.67; 95% CI: 0.50–0.90 for OS] (Norquist et al., 2018).

Trials using the *BRCAness* CGH signature have shown a benefit in *BRCAness*-positive patients treated with intensified platinum salts in an adjuvant setting (Schouten et al., 2015; Vollebergh et al., 2011). Vollebergh et al. (2011) observed a benefit of carboplatin in comparison to the conventional treatment (hazard ratio, 0.19; 95% CI: 0.08–0.48) in stage III HER2-negative BC patients with a BRCA-like CGH signature. This benefit was not observed in the BRCA-like negative patients (hazard ratio, 0.90; 95% CI: 0.53–1.54). Note that platinum regimens are not a standard of care in the BC adjuvant setting, and high-dose alkylating agents, a therapeutic class known to induce DNA damage similar to platinum salts, could act as a confounding factor.

The I-SPY 2 trial, a neoadjuvant multicenter, open-label adaptive phase 2 master protocol, evaluated two DNA repair deficiency signatures – PARPi-7 (a 7-gene expression signature) and a 77-gene *BRCAness* expression signature – in HER2-negative stage II or III BC patients. Both signatures were correlated with veliparib (a PARPi under development) – carboplatin response. In the veliparib–carboplatin arm, 41% of hormone receptor positive/HER2- and 75% of TNBC HRD patients achieved a pCR, *versus* 15% and 23% in the standard neoadjuvant chemotherapy control arm respectively (Wolf et al., 2017). These results are exploratory only, and the concordance between these two signatures appears moderate (64%; kappa = 0.29).

Genomic signatures, such as HRD–LOH, HRD–TAI, and HRD–LST, have been independently correlated with a high-level HRD score and platinum sensitivity in basal-like TNBC and HGSOC (Birkbak et al., 2012; Popova et al., 2012; Abkevich et al., 2012). According to Birkbak et al., a high HRD-TAI score is predictive of a pCR response to neoadjuvant cisplatin in TNBC patients (Birkbak et al., 2012).Moreover, the PreECOG 0105 phase II trial, testing a neoadjuvant association of carboplatin, gemcitabine, and iniparib in early TNBC, showed that the HRD–LOH score was associated with platinum response even if *BRCA1/2*-mutated tumors were excluded (Telli et al., 2015). These three scores demonstrated a significant correlation (Timms et al., 2014), allowing for elaboration of composite scores. In the Translational Breast Cancer Consortium (TBCRC) 009 trial, higher values for the HRD–LOH and HRD–LST combination score predicted platinum response in metastatic TNBC. This high composite HRD score was characterized with a high sensitivity but low specificity (because it identified some non-responders), while a low HRD score was strongly correlated with non-response (Isakoff et al., 2015). It is of note that the absence conventional chemotherapy control arm further contributed to the lack of specificity of the carboplatin response in this study (Isakoff et al., 2015).

Another combined score, the Myriad myChoice HRD score (Utah, USA) (incorporating HRD–LOH, HRD–TAI, and HRD–LST scores) was evaluated first as predictor of response to neoadjuvant platinum-based therapy in TNBC (Melinda et al., 2016). An elevated HRD score ≥42 was associated with a pCR to platinum salts in that cohort (OR, 6.52; p = 0.0058). The MyChoice HRD test also was evaluated in the abovementioned prospective TNT trial. Unfortunately, this HRD score failed to identify a subgroup deriving additional benefit from carboplatin over docetaxel (Tutt et al., 2018). One explanation for this

discrepancy might be that this genomic score is more predictive of chemosensitivity than of platinum-specific sensitivity. This hypothesis is supported by recent results showing that an elevated HRD score ≥42 is associated with a pCR to standard (anthracycline and/or taxane) neoadjuvant chemotherapy in TNBC (OR, 13.06; 95% CI: 1.52–11.241; p = 0.0028) (Telli et al., 2018).

Thus, the benefit of platinum compounds in the overall TNBC population appears low, and its use is not recommended, except in the cases of germline *BRCA1/2* mutations. In contrast to BC, platinum salts remain the backbone treatment of HGSOC, and a predictive biomarker for platinum salts has not been developed to date (Hillman and Lu, 2017).

3.3.2.2. Predictive biomarkers for PARPi. Preclinical findings have highlighted an increased sensitivity of *BRCA1/2*-deficient cells to PARP inhibition (Farmer et al., 2005; Bryant et al., 2005). This process, exploited in *BRCA1/2*-deficient cells, has been termed the "synthetic lethal strategy." It is based on cancer cell death induced by inactivation of two DDR pathways, whereas inactivation of one DDR pathway is not lethal. Indeed, PARP inhibition induces unresolved SSBs, unrepaired by BER (Ashworth, 2008), which are transformed into DSBs when the replication fork encounters them in S phase. To repair this damage, *BRCA1/2*-deficient cells use the NEHJ DNA repair pathway, which yields radial chromosome structure formation, inducing secondary cell death (Bryant et al., 2005; Farmer et al., 2005). Multiple PARPi, such as olaparib (AZD2281), rucaparib (CO-338), veliparib (ABT888), niraparib (MK4827), and talazoparib (BMN-673), are in various stages of clinical development either as single agents or in combination therapy for the management of EOC and BC.

BRCA1/2 mutations (germinal in metastatic BC, germinal or somatic in EOC) are validated predictive biomarkers of PARPi, with a high LOE. OlympiAD was a randomized, open-label phase 3 study that compared olaparib monotherapy *versus* standard therapy in 302 patients with germline *BRCA1/2* mutations and HER2-negative BC. The results showed an improvement in PFS, from 4.2 months to 7 months (hazard ratio, 0.58; 95% CI: 0.43–0.80; p = 0.009), in patients receiving olaparib compared with chemotherapy, with a concomitant doubling of the response rate in the olaparib group (59.9% *versus* 28.8%) (Armstrong et al., 2017). Results from a similar study, EMBRACA, testing talazoparib *versus* physician choice in advanced *BRCA1/2* germline-mutated BC, were presented at the 2017 SABC symposium. That study showed an improvement in clinical benefits in all subsets, with a median PFS from 5.6 months (4.2–6.7) to 8.6 months (7.2–9.3) (hazard ratio, 0.542; p = 0.0001) in patients receiving talazoparib *versus* chemotherapy (Litton et al., 2017). The efficacy of niraparib *versus* physician choice is under investigation in a phase III (BRAVO trial, NCT01905592) trial for HER2-negative BC.

In EOC, olaparib, niraparib and rucaparib have been approved by the US Food and Drug Administration (FDA) as maintenance treatment for relapsing patients having received and responded to two or more platinum-based therapies. This approval is based on results of a phase II trial in which olaparib as maintenance monotherapy following an initial response to a platinum regimen showed a PFS of 11.2 months *versus* 4.3 months with placebo (hazard ratio, 0.18; 95% CI: 0.10–0.31; p < 0.0001) in tumors harboring *BRCA1/2* germline and somatic mutations (Ledermann et al., 2012). The results from this study were the basis for the development of the subsequent phase 3 trials SOLO2 (olaparib)(Pujade-Lauraine et al., 2017), ARIEL3 (rucaparib)(Coleman et al., 2017) and NOVA (niraparib)(81) where PARPi were tested as a maintenance therapy in platinum sensitive EOC. In these trials, patients with BRCA1/2 germline or somatic mutation having received olaparib, rucaparib or niraparib had a longer PFS than did patient with placebo, with a median PFS of 16.6 to 21 months *versus* 5.4 to 5.5 months.

A small benefit with olaparib maintenance in patients without *BRCA1/2* tumor mutations was noted (7.4 *versus* 5.5 months; hazard ratio, 0.54; 95% CI: 0.34–0.85; p = 0.0075) (Ledermann et al., 2014), but no additional biomarkers studied in this population have been reported to date. In the olaparib monotherapy phase II trial, 24% of *BRCA*-negative patients affected by an EOC achieved an objective response on RECIST evaluation, raising once more the question of which is the more accurate biomarker for this HRD population (Gelmon et al., 2011).

In preclinical studies, methylation of the *BRCA1* promoter has been correlated to PARPi sensitivity (Veeck et al., 2010), and subanalyses in prospective trials seemed to confirm this hypothesis (Swisher et al., 2016). Dedicated clinical assays are needed to easily evaluate *BRCA1* methylation status, because next-generation sequencing technology cannot pick up this deficiency of *BRCA1* arising from promoter hypermethylation (Swisher et al., 2016).

The three genomic signatures (HDR–LOH, HRD–TAI, and HRD–LST) described above are under prospective clinical investigation, yielding conflicting results to date. The initial results of the ARIEL-2 multicentric prospective phase II trial have been recently published (Swisher et al., 2016). This trial assessed rucaparib sensitivity in three prospectively defined subgroups based on a score combining *BRCA* mutational status and LOH percentage in relapsed carboplatin-sensitive HGSOC (Swisher et al., 2016). Results suggested an increased PFS under rucaparib treatment within the *BRCA* 1/2 mutation group (hazard ratio, 0.27; 95% CI: 0.16–0.44; p < 0.0001) and in the high genomic LOH group (hazard ratio, 0.62; 95% CI: 0.42–0.90; p = 0.011) compared with the low-LOH cohort. The highest benefit was associated with the *BRCA1/2* mutation group. However, the clinical difference in term of PFS between the two *BRCA* wild-type subgroups did not seem to be relevant; the median PFS for the two wild-type subgroups was quite similar (5.7 months [5.3–7.6] in the LOH-high subgroup and 5.2 months [3.6–5.5] in the LOH-low subgroup). Moreover, this study could not determine prognostic and predictive respective values of this biomarker due to the lack of a control arm.

Mirza and colleagues (Mirza et al., 2016) recently published the results of a prospective multicenter phase III trial assessing niraparib maintenance therapy in platinum-sensitive recurrent ovarian cancer. They showed an increased tumor response and PFS for the niraparib arm compared to placebo, regardless of the *BRCA* and HRD status. In HRD-negative tumors, even if the response magnitude was smaller than in HRD-positive tumors, patients with EOC had a clinical benefit with a median PFS of 6.9 months *versus* 3.8 months.

Platinum sensibility seems to be a major predictive factor of PARPi efficacy. Platinum sensitive EOC treated with PARPi had an improved outcome regardless BRCA status with the magnitude of greater effect for BRCA mutated tumors according to Study 19, NOVA and ARIEL3 studies (Ledermann et al., 2012; Mirza et al., 2016; Coleman et al., 2017). In contrast, in platinum resistant EOC with germline *BRCA1/2* mutation the median duration of response with olaparib was 7 months (Kaufman et al., 2015). These results led to niraparib and rucaparib approval by the FDA as maintenance therapy in platinum sensitive EOC, irrespective of the status of *BRCA* mutations and/or HRD. For olaparib, the approval is only for *BRCA* carriers. For non-carriers, olaparib is currently under investigation in the phase IIIB OPINION study.

Concerning BC, there is little evidence of activity for unselected patients (Balmaña et al., 2014). In Gelmon et al.'s phase II study, no objective response was reported in sporadic TNBC under olaparib treatment (Gelmon et al., 2011). Studies evaluating PARPi as a single agent or in combination are ongoing in *BRCA1/2* mutated BC and in sporadic TNBC (Fasching et al., 2016; Livraghi and Garber, 2015). Considering the numerous putative biomarkers of HRD to be evaluated, it is mandatory to develop and validate predictive biomarker-based trials of PARPi within and beyond TNBC.

4. Discussion

Because of the potential toxicity of PARPi and platinum agents and to minimize overall medical care costs, an efficient biomarker should be

characterized by high PPV, helping the physician to select a population of patients with a high probability of response to the selected drug. Moreover, this test should show a high NPV to avoid missing potential responders, considering the lack of alternative efficient therapeutics in TNBC or EOC.

To date, it could be considered that outside of *BRCA1/2* germline mutations, a gold standard marker for *BRCAness* does not exist. Most of these putative biomarkers have not been compared in clinical trial based on large patient cohorts to identify the most useful in clinical practice, and few achieve a high LOE for clinical utility according to ASCO recommendations (Van Poznak et al., 2015). In fact, few biomarkers have been prospectively validated in a randomized controlled trial that includes a control chemotherapy arm (Table 3) and only somatic/germline *BRCA1/2* mutations appear to have good LOE (for platinum salts responsiveness and PARPi response) and could be used in clinical practice.

The genomic scar assays proved to be associated with a high NPV but not a high PPV of response to platinum salts and PARPi (Watkins et al., 2014). Moreover, in an HGSOC platinum-sensitive population, with a high rate of HRD tumors, the sensitivity of these assays seemed decreased (Watkins et al., 2014). The limits of these genomic scars are their static condition and their lack of dynamic evaluation over time. They represent the accumulation of ongoing and past DNA lesions. Resistance mechanisms to cisplatin or PARPi, such as *BRCA1/2* reversion mutations or the loss of 53BP1 (Sakai et al., 2008; Edwards et al., 2008; Jaspers et al., 2013), and independent mechanisms of resistance such as efflux pump overexpression, could be acquired after the development of aberrant chromosomal rearrangements. Moreover, some somatic mutations and epigenetic modifications could be more heterogeneous and reversible over time because of clonal selection and treatment pressure (Baylin and Bestor, 2002). An elevated HRD score would not be associated in such cases with a high PPV. To improve the PPV within the HRD population selected using genomic scars, another assay/method to detect secondary acquired resistance must be added (Watkins et al., 2014). It would be challenging to develop a strategy that could test for an ongoing repair process and not intuit a repair process on the sole basis of characteristic mutations. This alternative strategy could be based on functional tests (Mukhopadhyay et al., 2012); however, these assays appear difficult to implement in clinic (Mukhopadhyay et al., 2012).

Studies are ongoing to include PARPi in the initial treatment of EOC rather than only in maintenance. Association of PARPi and chemotherapy (platinum and paclitaxel *versus* chemotherapy alone (Oza et al., 2015) or cyclophosphamide (Kummar et al., 2015) showed an increased toxicity profile in earlier studies. To date there is no proof that the PFS benefit is due to the combination rather than the PARPi maintenance. At the same time, ways to overcome resistance to platinum salts and PARPi are investigated. These include work on contextual synthetic lethality strategies (which correspond to sensitization of HR proficient tumors with inhibiting HR agents to PARPi and platinum salts such as antiangiogenic agent (Liu et al., 2014), association of PARPi with inhibitors of cell cycle regulatory proteins or with other key proteins in HR pathway. Another interesting approach is the association of PARPi and immune checkpoints inhibitors which appears much easier to combine in the absence of cross toxicities (Lee et al., 2017), but needs additional clinical data.

5. Conclusion

The HRD phenotype is a complex association of genomic alterations, epigenetic changes, and phenotypic changes. To date, beyond *BRCA1/2* deleterious mutations, defining *BRCAness* remains challenging, and no strong LOE data have been published to guide clinicians in using an accurate biomarker. Determining a well-defined population requires new biomarkers or an association to improve their predictive values. The clinical utility of these biomarkers remains to be proven. It is critical to select the appropriate population to offer treatment with a lower toxicity and higher efficiency while reducing public costs. At the same time, research on PARPi and platinum salts is increasing and shows their multiple interactions with other molecularly targeted therapies, including inhibitors of immune checkpoints or anti-angiogenic agents. This new concept could lead to new biological models in which HR-proficient cells benefit from PARPi and platinum salts under concurrent targeting. Dedicated studies on this topic will be critical.

Conflict of interest statement

William Jacot and Charles Theillet declare research funding from AstraZeneca. Severine Guiu and Elodie Chartron have no conflict of interest to declare.

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